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RESEARCH ARTICLE

# FORMULATION OF CLOTRIMAZOLE ORORETENTIVE JELLY

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## ABSTRACT

**Objective:** Patient compliance and ease of administration are of significant importance in the design of dosage forms. Dysphasia is common among all age groups, especially in elderly and pediatrics. There are dosage forms like tablets, syrups in the market but still there is a need for new dosage form which acts effectively and locally. Jellies can provide an attractive alternative formulation in the treatment of oral candidiasis. So the present investigation aims to design, prepare and evaluate Clotrimazole jellies using xanthan gum with different concentrations. The benefits of these prepared jellies are increased bioavailability by-passing first pass metabolism.
**Method:** The sucrose based jellies were prepared by heating and congealing method. Physical characteristics, pH, syneresis, *in vitro* dissolution testing, drug release kinetics, IR Spectral analysis and stability studies were conducted.
**Result:** The prepared formulations are free from gritty particles. Among the prepared formulations, formulation $C_3$ containing 1.5% xanthan gum released 93.22% in 30min was found to be promising. Stability studies on the promising and other formulations indicated that there were no significant changes in the drug content and *in vitro* dissolution characteristics. IR spectroscopic studies indicated that there were no drug-excipient interactions. Anti-fungal studies revealed that there is no change in the molecular activity of the drug.
**Conclusion:** The prepared jellies of Clotrimazole could stay in the mouth for a longer period of time, which indicates a potential use of jellies of Clotrimazole for treating oral candidiasis.
**Keywords:** Clotrimazole; Jellies; Xanthan gum.

## INTRODUCTION

Oral candidiasis is one of the common fungal infections, affecting the oral mucosa. Candidiasis is defined as an infection caused by a fungi of the genus *Candida*, and the term oral candidiasis is only used when describing a clinically visible lesion in the oral cavity.[1]These lesions are caused by the yeast *Candida albicans*. The most prevalent Candida species involved in human infection is *C. albicans*. In oral candidiasis, *C. albicans* generally accounts for around 50% of cases.[2,3] In the acquired human immunodeficiency syndrome (AIDS), it is known that among the opportunist infections, oral candidiasis is the most frequent one, and *C. albicans*, among others, has been very important in assessing the evolutionary behavior of the disease.[3]The first case of acquired human immunodeficiency syndrome (AIDS) related in the literature mentions that the patient was an oral candidiasis carrier.[4] In human immunodeficiency virus (HIV+) patients, nonspecific oral immunity is reduced, contributing to the frequent appearance of candidiasis.[5,6] Better stability and longer residence time will allow more of the antifungal to penetrate through the oral mucous layer to act on *Candida* species for longer duration of time. One way to improve the efficacy in eradicating the infection is to deliver the antifungal drug locally in the oral cavity. Therefore some researchers had prepared and reported new formulation such as gels, mucoadhesive tablets, pH sensitive excipients composition mucoadhesive microspheres, which were able to reside in oral cavity for an extended period for more effective candidiasis eradication.[7]The present investigation is designed to improve patient compliance and ease of administration. Advantages of the Clotrimazole jellies as dosage forms include increase in bioavailability, reduction in dose size, and in gastric irritation, bypass first pass metabolism. The present work is aimed at preparing a formulation of Clotrimazole jellies, for relief of oral candidiasis.

## MATERIALS AND METHODS

Clotrimazole was received as a gift sample from M/s Alkem Laboratories Pvt. Ltd., Mumbai. Xanthan gum was obtained from Local market. Sucrose was brought from SD Fine Chemicals, Mumbai. Citric acid was received from CDH Pvt. Ltd., Mumbai. All other chemicals and solvents used are of analytical grade and used as procured.

### Preparation of Medicated Jellies [8]

All the formulations were prepared using freshly boiled and cooled distilled water as per the composition listed in Table 1. Clotrimazole jellies were prepared by heating and congealing method. Syrupy base was prepared in a copper vessel dissolving the required amounts of sugar in water on heating and stirring at 80°C for about 90 min. accurately weighed polymer powder was dispersed in 10 mL of purified water maintained at 90°C throughout preparation. The dispersion was stirred using a magnetic stirrer (2MLH, Remi Equipment Pvt. Ltd., Mumbai, India) for 20 min to facilitate hydration of gelling agent. Clotrimazole was taken in another beaker and solubilized using alcohol. Then simple syrup was added to it under continuous stirring. Then citric acid and preservatives were added under continuous stirring. Color and flavor was added to this under continuous stirring at 60°C. The final weight was adjusted with purified water, mixed, transferred to polyethylene molds, sealed and allowed to cool at room temperature (25°C ± 5°C) to form a jelly like texture. After the jelly is set it is wrapped in to the gelatin paper and store in dry place.

**Table 1: Working formulae to prepare Clotrimazole jellies[20]**

| Sl. No | Ingredients (w/w) | $C_0$ | $C_1$ | $C_2$ | $C_3$ |
|---|---|---|---|---|---|
| 01 | Drug | 0.2 | 0.2 | 0.2 | 0.2 |
| 02 | Xanthan gum | - | 0.5 | 1 | 1.5 |
| 03 | Citric acid | 1 | 1 | 1 | 1 |
| 04 | Alcohol | 5 | 5 | 5 | 5 |
| 05 | Methyl paraben | 0.18 | 0.18 | 0.18 | 0.18 |
| 06 | Propyl paraben | 0.02 | 0.02 | 0.02 | 0.02 |
| 07 | Color | Q.S | Q.S | Q.S | Q.S |
| 08 | Flavor | Q.S | Q.S | Q.S | Q.S |
| 09 | Sucrose | 66.7 | 66.7 | 66.7 | 66.7 |
| 10 | Purified water | 28.8 | 28.8 | 28.8 | 28.8 |
| 11 | Total weight | 100 | 100 | 100 | 100 |

* Each jelly contains 10 mg of Drug. * Each jelly weighs 05 gm.

### Characterization of prepared clotrimazole jellies

### Physical observation[9]

The prepared jellies were observed visually for clarity, odor, texture and presence of any gritty particles. The texture was evaluated in terms of stickiness and grittiness by mild rubbing the jelly between two fingers.

### Weight variation[10]

The average weight of ten jellies was taken to determine weight variation. The jellies were taken out of the molds in a beaker and weighed individually, pooled and mixed.

### Determination of pH[11, 12]

The pH of the formulation influences the taste and stability of oral jellies. The pH of prepared jellies was measured using a digital pH meter (LI 120, Elico Ltd., Hyderabad, India) at room temperature (25°C ± 5°C). For this purpose, 0.5 g of jelly was dispersed in 50 mL of distilled water to make a 1% solution, and the pH was noted.

### Syneresis[13]

Syneresis or de-swelling is usually seen in gels due to the release of liquid, resulting in shrinkage of gels and reduce quality. Syneresis is the contraction of the gel upon storage and separation of water from the gel. It is more pronounced in the gels, where lower concentration of gelling agent is employed. All the jellies were observed for signs of syneresis at room temp (25°C ± 5°C). The formulations showing signs of syneresis were rejected and not considered for further studies.

### Drug-Excipient Compatibility Studies[14]

The drug and excipients were mixed together in 1:1 ratio and placed in borosilicate colored glass vials. These vials were sealed and placed in an oven maintained at 40°C and 75% RH. The samples were observed after 15, 30 and 45 days for any color change or lump formation. Fourier transforms infrared (FTIR) spectra of the pure drug and its mixtures of gelling agents were measured by preparing dispersion in dry KBr using attenuated total reflectance FTIR spectrophotometer (Bruker, UK). The absorption maxima in the spectra obtained were compared, and the presence of additional peaks corresponding to the functional groups was noted.

### Stability Studies[15, 16]

A physically stable medicated oral jelly should retain its viscosity, color, clarity, taste, and odor throughout its shelf-life. The stability studies were performed at two temperatures i.e., 37°C and 45°C over a period of six months. Sufficient number of samples (10) were packed in amber colored screw capped bottles and kept in incubator maintained at 37°C. Samples were taken at intervals of 15 days for the drug content estimation.

### *In Vitro* Drug Dissolution Studies[17, 18]

USP XXIII Dissolution test apparatus was used by taking 100 ml of pH 6.8 buffer in 1000 ml dissolution flask and jelly was placed in it, rotating paddle at a speed of 150 rpm and temperature 37±1ºC was maintained. 5 ml aliquots were withdrawn at 01, 02, 03, 04, 05 and 06 minutes intervals, after each withdrawal of a sample an equal volume of dissolution medium was

added to the dissolution flask. The filtered samples were diluted and analyzed spectrophotometrically at 272.0 nm.

### Antifungal Activity[19]

Microbiological studies were carried out to ascertain the antifungal activity of the prepared formulation as against the pure drug. Clotrimazole is known to possess superior antifungal activity against fungal infections. In present work, antifungal activity of clotrimazole was tested by using the yeast *Candida albicans*, which is the most frequently encountered human fungal pathogen being responsible for a wide range of superficial infections. The prepared jellies were evaluated for *in vitro* antifungal activity using standard Agar cup-plate method.

## RESULTS AND DISCUSSION

### Characterisation of Prepared Clotrimazole Jellies

### Physical observation

Physical observation of jellies is important to justify the patient acceptance and compliance of the products. The observed parameters are summarized in Table 2.of all the formulations $C_3$ showed best results being transparent and slightly sticky with an acceptable consistency.

**Table 2: Physicochemical parameters of Clotrimazole jellies**

| Formulations | Properties of jellies | | | | |
|---|---|---|---|---|---|
| | Appearance | Consistency | Texture | pH of the jelly | Syneresis (Room temp: $25^0$C± $5^0$C) |
| $C_0$ | Transparent | Slightly liquid | Non-sticky | 6.51±0.03 | - |
| $C_1$ | Cloudy | Acceptable | Sticky | 6.25±0.05 | - |
| $C_2$ | Cloudy | Acceptable | Slightly sticky | 6.32±0.08 | - |
| $C_3$ | Transparent | Acceptable | Slightly sticky | 6.93±0.01 | - |

* Each reading is a mean of three replicates.
* Each jelly contains 10 mg of Clotrimazole
* Each jelly weight of 5 gm
* + positive; - negative

**Table 3: Antifungal studies showing the comparative zone of inhibition of drug as pure and in formulation ($C_3$)**

| Formulation Code | Statistical Zone inhibition (mm) after 36 hrs | | | Mean± S.D |
|---|---|---|---|---|
| | Zone 1 | Zone 2 | Zone 3 | |
| Pure Drug | 23 | 23 | 24 | 23.33±0.57 |
| $C_3$ | 24 | 23 | 24 | 23.66±0.53 |

### Weight variation

The weight variation was found between 4.97%±0.84% and 5.73%±0.63% in all prepared jelly formulations.

### Determination of pH

The results of pH of prepared jelly formulations are summarized in Table 3. The pH of the formulation influences the taste and stability of oral jellies. The pH of the prepared formulations was found in the range of 6.25±0.02-6.93±0.03 which was slightly acidic. Sucrose may precipitate in the presence of citric acid on standing. Therefore, a minimum quantity of citric acid was added just to maintain the pH.

### Syneresis

Syneresis observed after 24 h of jelly preparation. None of the formulations showed syneresis at room temperature (25°C ± 5°C) (Table 2).

### Stability studies

The samples were characterized for change in various parameters such as appearance, pH, sugar crystallization, stiffness, syneresis and drug content at the end of 90 days. A freshly made sample was used as a reference standard for subjective evaluations. Formulation $C_3$ showed best results.

### In vitro dissolution testing

The *in vitro* dissolution study was carried out to compare clotrimazole release kinetics from the prepared formulations. The results are summarized in Figure 1. $C_3$ showed optimal results.

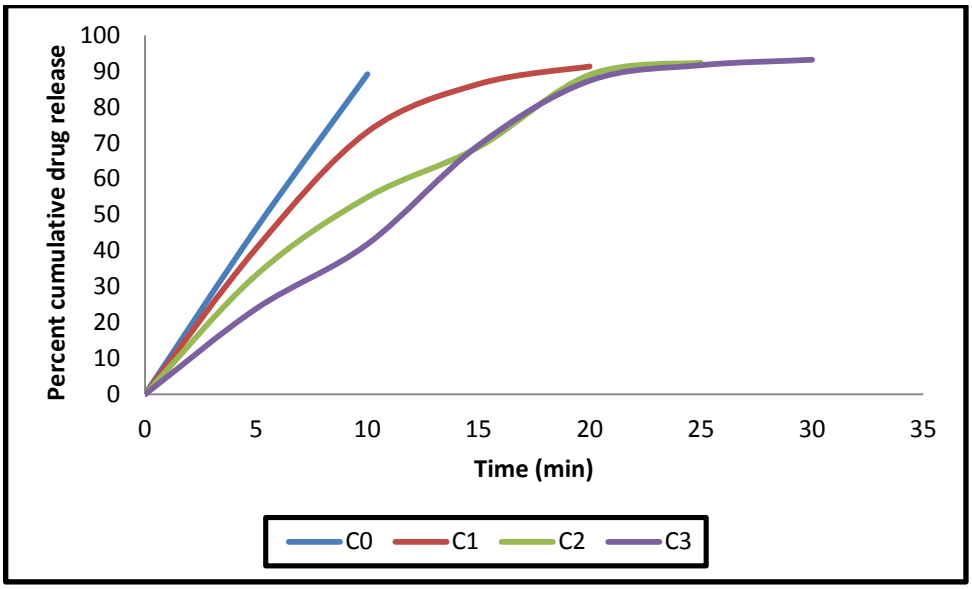
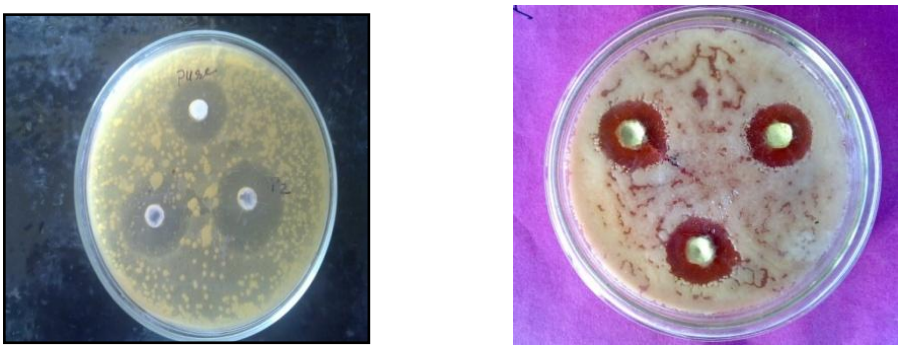



**Figure 1: *in vitro* studies of Clotrimazole medicated jellies**

*All values are in triplicates *Each jelly contains 10 mg of Drug. *Each jelly weighs 05 gm.



Pure drug $C_3$

**Figure 2: Photographs of antifungal studies showing the comparative zone of inhibition of drug as pure and in formulation ($C_3$)**

## Antifungal studies

The anti-microbial study reveals that zone inhibition of promising formulations was found to be equal on comparison with the activity of pure drug. This indicates that there is no change in the molecular activity of the drug present in the formulations. The results are summarized in table 3.

## CONCLUSION

It is found that sucrose based Medicated jellies will be ideal dosage forms for elderly and pediatrics patients. These will have additional advantages of efficient treatment including low dose, ease of administration, immediate onset of action, reduced dosage regimen and economic. The Physico-chemical characterization revealed that all the formulations were found to be shown acceptable weight variation, pH and syneresis. The drug content estimation showed uniform drug content in all the formulations. IR spectroscopic studies indicated that there were no drug-excipients interactions. Addition of polymers like xanthan gum yield good results to prolong dissolution time and the drug release in salivary pH conditions for a period of 30 minutes. The stability studies proved that the prepared Medicated jellies were found to be stable when stored at air tight containers or twist strips. The antifungal study reveals that zone inhibition of various prepared formulations was found to be equal on comparison with the activity of pure drug. This indicates that there is no change in the molecular activity of the drug present in the formulations. The present work on Medicated Jellies offer patient convenience and compliance and ease of administration in application.

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